UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	18

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

	Application No.	Applicant(s)	
Office Action Summary	09/529,458	SHORT, JAY M.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2001*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20 and 22-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20 and 22-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ [illegible]
4) ☐ Interview Summary (PTO-413) Paper No(s). ____
5) ☐ [illegible]

DETAILED ACTION

This action is in response to the amendment filed 20 August 2001 in which claims 16, 17, 19, 20, 22, 23, 25, 27, 29, 33, 36 and 38-47 were amended, claim 21 was cancelled and new claim 48 was submitted. It is noted that in the clean version of the claims in the amendment filed 20 August 2001, claims 18, 24, 26, 28, 30-32, 34, 35 and 37 have been labeled "amended" however no amendments to these claims is evident, and they are not provided in the marked up version of the claims.

Any rejection from any previous action not repeated herein has been withdrawn.

Claims 16-20 and 22-48 are pending.

Response to Amendment

Claims 36-37 and 42-48 stand rejected under 35 U.S.C. §112, first paragraph with respect to the lack of enablement for in vitro, for reasons of record and as further discussed below. This rejection has been extended to the amended and new claims as discussed below.

Claims 45-47 stand rejected under 35 U.S.C. §112, first paragraph for reasons of record and as further discussed below.

Claims 16-20, 22-32 and 36-45 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Erickson et al in view Stein et al (1996 J. Bact. 178:591-599) and Horikoshi (1995 Curr. Op. in Biotech. 6:292-297).

Claims 16-20, 22-33 and 36-45 stand rejected under 35 U.S.C. §103(

Claims 16-20, 22-32 and 36-47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Erickson et al in view Stein et al (1996 J. Bact. 178:591-599) and Horikoshi (1995 Curr. Op. in Biotech. 6:292-297), and further in view of Patanjali et al (1991 Proc. Natl. Acad. Sci. 88: 1943-1947).

New rejections as necessitated by Applicant's amendment filed 20 August 2001 are detailed below under the heading "New Rejections and Objections".

Drawings

1. Applicant requests deferment of the filing of formal drawings until Applicant receives a Notice of Allowance. This request is granted. Applicant states that the drawings submitted comply with 37 CFR §1.83(a); this is correct in view of the amendments to the claims and this objection is withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-20, 36-37 and 42-48 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for performing the method in a cell, and with gene expression of a reporter gene as the basis of the detectable signal, does not reasonably provide enablement for performing the [illegible]

either type of detectable signal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation. This rejection has been extended to 42-47, which have been amended to now depend from claim 36, and new claim 48.

Applicant's arguments filed 20 August 2001 have been fully considered but they are not persuasive. Applicant states that in vitro gene expression or "cell-free" systems have been known for over a decade and that one of skill in the art would know how to carry out the invention in vitro based on teachings known to those of skill in the art and based upon the teachings provided in the specification. As stated in the action mailed 8 November 2000, the specification does not provide *any* teachings on how to perform the method in vitro. In the complete absence of teachings in how to perform the method in vitro, the specification cannot be considered enabling to use the invention in vitro.

With respect to the use of non-gene-based reporter systems, Applicant argues that non-gene based detectable systems were known in the art and that the specification teaches the quenching and fluorescence effects of GFP molecules in close proximity. This argument is not persuasive. The specification merely teaches that GFP mutants can be generated that have increased fluorescence resonance energy transfer between flanking GFP's. The specification however does not specify any particular mutants having the cited phenotype. Furthermore, the specification does not teach how such GFP molecules can be used to control growth of the cell. The general [illegible]

3. Claims 45-47 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

Applicant's arguments filed 20 August 2001 have been fully considered but they are not persuasive. Applicant argues that the amendments to the claims overcome this rejection. This is not correct. It is entirely unclear how the steps recited in claims 45-47 related to the steps recited in claim 36 as claim 36 does not recite "an environmental sample". The rejection is maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 16-20, 22-32, 36-45 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Erickson et al in view Stein et al (1996 J. Bact. 178:591-599) and Horikoshi (1995 Curr. Op. in Biotech. 6:292-297).

6. Claims 16-20, 22-32 and 36-45 stand rejected under 35 U.S.C. §103(a) as being

7. Claims 16-20, 22-32 and 36-47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Erickson et al in view Stein et al (1996 J. Bact. 178:591-599) and Horikoshi (1995 Curr. Op. in Biotech. 6:292-297), as applied to claims 16-20, 22-32 and 36-45, and further in view of Patanjali et al (1991 Proc. Natl. Acad. Sci. 88: 1943-1947).

Applicant's arguments filed 20 August 2001 have been fully considered but they are not persuasive for any of these rejections under 35 USC §103. Applicant argues that there is no suggestion to combine the references and that the rejections are based upon hindsight reasoning.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the [illegible] in the knowledge generally available to one of ordinary skill in

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is found both in the references themselves and in the knowledge available to one of ordinary skill in the art. Erickson et al teach the use of genomic expression libraries to screen for inhibitors for interacting molecules as such inhibitors are candidates drugs for pharmaceutical use. Horikoshi teaches that novel bacteria such as thermophiles represent a new source of new drugs including antiobiotics and bacterially active substances. Stein et al or Short et al teach making expression libraries from mixed populations of uncultivated organisms. At the time of the invention, the ever-present need to find new sources of possible drugs, which has been intensified by high efficiency and high-throughput screening technologies (see for instance Thompson et al (USP 5,824,485)) would motivate one of skill in the art to use sources of new and novel molecules such as the organisms taught by Horikoshi and to use libraries from mixed populations of such organisms as taught by Stein et al or Short et al in the method taught by Erickson et al to identify new possible drug candidates. Therefore, these rejections are maintained.

NEW REJECTIONS AND OBJECTIONS

Specification

8. The disclosure is objected to because of the following informalities: the amendment to p. 39, lines 21-28 lacks the serial number 08/876,276 which was amended into this section in the preliminary amendment filed [illegible]

Claim Objections

9. Claims 22 and 48 are objected to because of the following informalities: In claim 22, the "are" in line 4 should be the singular "is". In claim 48, the "are" in line 4 should be the singular "is". In claim 48, "identified" is misspelled in the first line of step ii. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. Claim 48 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 48 is drawn to a method for identifying a molecule that affects the interaction between a first and second molecule. At least one of the first or second molecules is derived from a library and is therefore itself unknown; if both are derived from a library, both are unknowns. The interaction in the presence of an unidentified molecule results in a detectable response and is compared to the response in the absence of the unidentified molecule. The method thus may identify an unknown molecule which affects the interaction of a known and another unknown molecule. The specification does not teach a use for an unknown molecule that affects the interaction of a known molecule and another unknown molecule, or a use for an unknown molecule which affects the interaction of two unknown molecules. One skilled in the art would

interaction cannot be taught by the prior art, so a use for a molecule affecting such an interaction cannot be enabled by the prior art. There are no working examples encompassed by this claim. Therefore, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method for identifying a molecule that affects the interaction between a first and second molecule.

11. Claims 33-35 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection. Claim 33 recites "enriching the environmental sample for eukaryotic organisms and selecting against prokaryotic organisms". While the specification provides support for enriching an environmental sample for prokaryotic organisms (p. 16, line 12 – p. 17, line 2), it does not provide support for enriching a sample for eukaryotic organisms. Therefore, the specification does not describe the claimed method in such full, clear, concise and exact terms so as to indicate that Applicant has possession of this method at the time of filing the present application. Thus, the written description requirement has not been satisfied and the new matter must be removed from the claims.

12. The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly

13. Claims 16-20 and 22-48 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is vague and indefinite in reciting "nucleic acid derived from a mixed population" as the nature and number of derivative steps is unknown. This rejection would be overcome by amend the claim to recite "nucleic acid obtained from a mixed population".

Claim 16 is vague and indefinite for reciting "a first interaction molecule and a second interaction molecule" in lines 7-8. Are these different from the "interaction molecules" recited in line 4?

Claim 16 is vague and indefinite because the recitation of "the first and the second molecules in the absence of the third molecule produces a detectable signal" is only partially consistent with the preceding recitation of "a cell containing interaction molecules which generate or repress a detectable signal or growth of the cell". What role does the recited repression play?

Claim 16 recites the limitation "the response" in line 13. There is insufficient antecedent basis for this limitation in the claim.

Claim 22 is vague and indefinite in reciting "a host cell". Is this host cell related to the cell recited in claim 16?

Claim 23 is vague and indefinite as the third gene encoding the third molecule is already expressed according to claim 16

Claims 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: expression of the first and second genes.

Claim 27 recites the limitation "the environmental library" in line 1. There is insufficient antecedent basis for this limitation in the claim, with respect to claim 16.

Claim 36 is vague and indefinite in reciting "a third molecule derived from a library" as the nature and number of derivative steps is unknown. This rejection would be overcome by amend the claim to recite "a third molecule encoded by a library".

Claim 36 recites the limitation "the...genomic DNA" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 36 is vague and indefinite as being incomplete. Claim 36 recites two possibilities in step (i): 1) "in the presence of a third molecule" and 2) "in the presence of the library or genomic DNA". While the claim recites further steps with respect to the third molecule, it does not recite any steps with respect what is to be done when the first and second molecules are contacted "in the presence of the library or genomic DNA".

Claim 36 is vague and indefinite in reciting "a molecule" in line 11. Is this molecule different from "the third molecule"?

Claim 42 is vague and indefinite in reciting "the molecule" as it is unclear to which molecule recited in claim 36 this refers.

Claims 45-47 are vague and indefinite it is entirely unclear what the recited steps have to do with the steps recited in claim 36 since claim 36 does not recite "environmental sample".

Claim 47 is vague and indefinite as it is unclear which nucleic acids are to be inserted into the expression vector: the isolated one recited in former step I or the amplified ones recited in former step L.

Claim 48 is vague and indefinite in reciting "molecule is derived from a library" as the nature and number of derivative steps is unknown. This rejection would be overcome by amend the claim to recite "molecule is obtained from a library".

Claim 48 is vague and indefinite in reciting "a molecule" in line 11 as it is unclear how this molecule is related to "an unidentified molecule" recited in lines 5-6.

Claim Rejections - 35 USC § 103

14. Claims 16-20, 22-33 and 36-45 are rejected under 35 U.S.C. §103(a) as being unpatentable over Erickson et al in view of Short et al (WO 97/04077) and Horikoshi, and further in view of Mendelsohn et al (Curr. Op. in Biotech. 1994 5:482-486. Erickson et al in view of Short et al and Horikoshi do not disclose the use of green fluorescent protein for the detectable response. Mendelsohn et al teaches the use of green fluorescent protein as a detectable gene in two hybrid methods used to find compounds that modulate protein interactions. See p. 485. first column. At the time the invention

for identifying a molecule which modulates the interaction between a first and second molecule. One of ordinary skill in the art would have been motivated to do this because Mendelsohn et al is a review article of the applications of two-hybrids systems, and the use of green fluorescent protein is suggested specifically in reference to finding compounds which modulate protein interactions by using two-hybrid systems such as those of Erickson et al. Furthermore, the use of green fluorescent protein is well known in the art for use as a reporter gene.

Conclusion

Claims 16-20 and 22-48 are rejected. Claims 33-35 and 48 are free of prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

November 5, 2001